Antivirals

Introduction

There are many viruses, as you may have surmised learning up to this point. The thing is, most viruses cannot be treated. Most are acute, run their course, and die out. Latent infections go dormant between acute attacks. Antivirals for acute viruses would do little, except perhaps shorten the duration of symptoms (as we do for influenza, HSV, and VZV)—they do not eliminate the virus. Those viruses that can become chronic infections are the ones we have treatments for. But even then, we don't necessarily treat a chronic infection unless it becomes symptomatic from profound immunocompromise (like we do for CMV). So, when it comes down to it, there are really only three viruses that we need to treat—hepatitis B, hepatitis C, and HIV. We start with the treatment of the herpesviruses, then transition through the three chronic viruses that deserve more attention.

Mechanisms

There are infinite names to learn in this space. But there are only **five classes** of medications. Even though there are so many drug names, what becomes apparent is a recurring theme—most of our therapies target polymerases. Depending on the virus, that polymerase could be DdDp, DdRp, RdDp, or RdRp. When we target polymerases with medications, there can be drugs that inhibit by being a nucleoside analog (**nucleoside analog polymerase inhibitors**) and those drugs that inhibit the polymerase by any other means (**NON-nucleoside analog polymerase inhibitors**).

As we progress through the lesson we'll add mechanisms. And that is why the lesson is set up the way it is, herpesvirus first, then hepatitis B, because in both, we treat only the polymerase. Hepatitis C introduces the concept of a protease inhibitor. Then HIV finishes it off with the addition of fusion inhibitors and integrase inhibitors.

VIRUS (POLYMERASE)	NUCLEOSIDE ANALOG POLYMERASE INHIBITOR	NON-NUCLEOSIDE ANALOG INHIBITOR	PROTEASE INHIBITOR	FUSION INHIBITOR	INTEGRASE INHIBITOR	OTHERS
HSV, VZV (DdDp, DdRp)	Acyclovir Valacyclovir	Foscarnet	N/A	N/A	N/A	N/A
CMV (DdDp, DdRp	Ganciclovir Valganciclovir	Foscarnet	N/A	N/A	N/A	N/A
Hep B (RdDp)	Lamivudine Entecavir Tenofovir Adefovir	N/A	N/A	N/A	N/A	Interferon Ribavirin
Hep C (RdRp)	N5SB-Pol-i Sofosbuvir	NS5B-Pol-i Dasabuvir	NS3/4A-Pro-i Grazoprevir	N/A	N/A	NS5A-i Velpatasvir Ledipasvir
Old school HIV (RdDp)	Lamivudine Zidovudine Abacavir	Rilpivirine	Darunavir/r Atazanavir/r	Maraviroc Enfuvirtide	Raltegravir	N.A
HIV (RdDp)	Tenofovir Emtricitabine	Efavirenz				

Table 8.1: Summary of Drugs Organized by Their Mechanisms of Action and the Virus They Treat
All protease inhibitors are boosted with 100 mg of ritonavir, abbreviated as "drugname/r."

Whenever we administer an antiviral, we want it to go to **virally infected cells only**. That way, we kill bad cells and bad viruses while leaving good cells alive and well (read: minimize side effects). After all, all viruses are DNA or RNA. So are we. Anything we give as a drug should either **not work on our enzymes** (targeting instead an enzyme the virus codes for) or be a **prodrug that gets activated only in virally infected cells** (activated by an enzyme the virus encodes for). And we design drugs with similar mechanisms of action to fight specific viruses because we rely on the viral proteins to turn them on, and each virus family has a different set of viral proteins. Mechanisms are similar; drugs are different.

Medications Used to Treat Influenza

We covered this briefly in Viruses #5: *ss(–)RNA Viruses*, and do not go into detail here. They are also way outside the five mechanisms we want you to learn in this lesson. M2 protein uncoating inhibition (amantadine) does not work. Neuraminidase inhibitors (oseltamivir) might decrease symptom duration, but probably don't work, either. Get your flu shot.

Medications Used to Treat Herpesvirus Family—Polymerase

The key to recognizing an anti-herpesvirus-family drug is to identify the cyclic part of the name (cyclo, ciclo) and antiviral suffix (-vir). A-cyclo-vir, gal-cyclo-vir, pen-ciclo-vir are all examples.

Herpes family viruses are HSV, VZV, and CMV. That's it, those three. Yes EBV, HHV6, and HHV8 are also herpes family viruses. But we don't treat those. Keep this simple. Three meds, three viruses.

When we tack "val-" to the front of a drug name, it indicates improved oral bioavailability. Acyclovir and ganciclovir are prodrugs, converted to the active compound by viral-encoded proteins. Valacyclovir and valganciclovir are proprodrugs. When a human ingests the proprodrug as a pill, first-pass metabolism by the liver biotransforms the proprodrug into the prodrug before it gets to systemic circulation. Metabolism by the liver on first pass is turned into the prodrug, effectively delivering more prodrug to systemic circulation than if the prodrug were taken as a pill (where the liver would metabolize the prodrug to an inactive metabolite). That is great for taking IV medications and turning them oral; it is a pharmacologic mechanism to deliver more of the drug we want in the person's systemic circulation to that person's systemic circulation through the route of oral ingestion. It is a convenience factor only. In terms of mechanism of action, indications, and side effects, valmedication and medication are the same, so we discuss (val)acyclovir, (val)ganciclovir, and foscarnet.

Acyclovir and valacyclovir are **nucleoside analogs** (guanosine). Guanosine is used in RNA and DNA. HSV and VZV are DNA viruses. Both transcription (RNA polymerase, DdRp) and replication (DNA polymerase, DdDp) can be affected. The reason we can use these medications to treat HSV and VSV specifically is because they possess a **viral thymidine kinase** that is expressed only in infected cells. The only location the prodrug will be activated into the active drug is in infected cells with transcriptionally active viruses. The prodrug is distributed everywhere, but only in infected cells do viral proteins activate the prodrug into the active compound. The drug looks like guanosine, except that it **doesn't have a pentose sugar** (the acyclo part). The active compound, **acyclo-GTP**, also has a **higher affinity** for both RNA polymerase and DNA polymerase than the normal **dGTP**. So, as the virus tries to transcribe RNA or replicate DNA, acyclo-GTP gets incorporated into a growing strand. The pentose sugar of the active compound is connected to the growing strand, 5' P to the strand's 3' OH group. When the next nucleotide tries to get added to the growing strand, its 5' phosphate encounters . . . no 3' OH. No 3' OH, no elongation. The result is **chain-length termination**. These medications are generally well tolerated because they are activated only in viral-infected cells. However, **resistance** can be developed simply by **eliminating viral thymidine kinase**, the first step necessary for prodrug to active drug conversion. Oral acyclovir is used for mucosal (HSV) and cutaneous (VZV) outbreaks, shortening symptom duration. IV acyclovir is used for HSV encephalitis. However, **CMV doesn't have thymidine kinase**, so cannot be treated with these drugs.

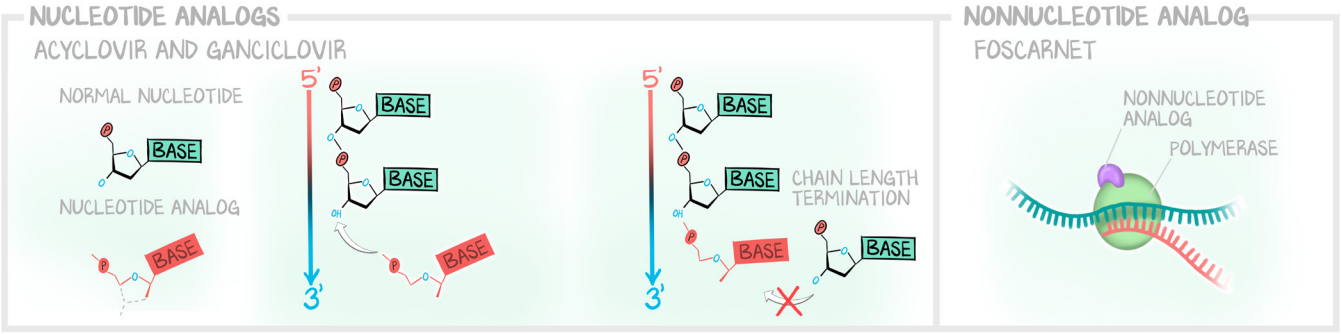

Figure 8.1: Mechanisms of Action
Nucleotide analogs have similar structures to nucleotides. Acyclovir has no cyclic sugar, no 3'OH to add the next nucleotide, causing chain length termination. Others may have an abnormal base. In all cases, the nucleotide analogs are used by the polymerase (in this case DNA polymerase and RNA polymerase) to cause disruptions of viral replication and viral protein transcription by becoming incorporated as a nucleic acid. Non-nucleotide analogs bind to the polymerase but separate from the site that grows the nucleic acid chain. In the case of herpesviruses, foscarnet is the example.

Ganciclovir and valganciclovir are **also nucleoside analogs** (guanosine). Guanosine is used in DNA and RNA. Acyclo-GTP is the mechanism, chain-length termination, RNA polymerase, and DNA polymerase. Great. So, they are just another acyclo-variant, right? Sort of. They can be used to treat HSV and VZV because they are **activated by viral thymidine kinase**, just like their cousins. However, these versions **do fight CMV**. Even though CMV doesn't have a thymidine kinase, ganciclovir offers an alternative method of activation from prodrug—**phosphotransferase**—an enzyme CMV-infected cells do express. That sounds like a real win, and since it works for VZV and HSV, why don't we just use this all the time? For a while, ganciclovir was available only in the intravenous formulation, so it had to be used for severe cases only. Since the advent of **oral valganciclovir**, intravenous administration has precipitously dropped. It still isn't the go-to, for three reasons. One, CMV rarely causes disease except in profound immunocompromise, so needing ganciclovir is rare. Two, HSV and VZV should be treated with the less toxic, more narrow-spectrum cousins to prevent resistance by CMV. CMV is in 90% of people. It doesn't cause disease until profound immunocompromise. If we treat nonlethal non-CMV infections with a drug that does affect CMV, the CMV will become resistant to the CMV medication, and if the patient becomes susceptible to CMV, CMV will already be resistant. If antibiotic stewardship wasn't enough, the real kicker is three: the **prodrug can also be activated by human cells**, which means the side effects are worse by far than with its predecessors. Those cells that have **the highest turnover** get affected the most, and it happens to be **bone marrow suppression** that limits the drug's use.

Foscarnet is not a nucleoside analog, but it is a polymerase inhibitor, making it a **non-nucleoside** analog polymerase inhibitor, and that's why it is a drug that breaks the mold on the naming game—no ciclo and no vir. Foscarnet also inhibits viral polymerases (DdRp, DdDp), but is not incorporated into the growing chain. It is given **intravenous only, causes hypocalcemia and hypomagnesemia**, and has no bone marrow suppression, but is **nephrotoxic**. It is chosen only when there is resistance to the acyclos or bone marrow suppression limits their use.

HSV OR VZV	CMV	DRUG OF LAST RESORT
Acyclovir	Ganciclovir	Foscarnet
Valacyclovir	Valganciclovir	N/A
Thymidine kinase	Thymidine kinase phosphotransferase	N/A
Little risk	Bone marrow suppression	Nephrotoxic, IV only

Table 8.2
Acyclovir for VZV and HSV infections, limited side effects. Ganciclovir to treat CMV. If you have a resistant strain of HSV, VZV, or CMV, OR there is bone marrow suppression while trying to treat CMV, use foscarnet.

Drugs Used to Treat Hepatitis B

For a long time we looked at hepatitis B as Hepatitis Virus. We treated hepatitis B like we treated hepatitis C—interferon and ribavirin. Neither is targeted therapy and both attack general viral principles. The treatment was awful for patients (laden with side effects), and rarely worked. When we started paying attention to the viral mechanisms, we found that hepatitis B, which has a reverse transcriptase, could be targeted like we do another virus with reverse transcriptase—HIV. Since ribavirin and interferon are essentially eliminated from Hep C treatments (see the next section), we will discuss these agents here. However, the more effective way to treat hepatitis B is to use the same antiretrovirals we use for HIV.

Ribavirin. Ribavirin is a . . . get ready for it . . . **guanosine analog**, just like the acyclos that treat herpesvirus. Only this guanosine analog isn't an acyclo—it is NOT missing the cyclic pentose sugar. It inhibits a polymerase AND messes up mRNA. It exerts its antiviral effects by inhibiting guanosine triphosphate formation, preventing **viral mRNA capping** (the transcript cannot leave the nucleus without a 5'-methylguanine cap), and by directly inhibiting **RNA polymerase** (DdRp). It stops the ability of the virus to make viral mRNAs. Hepatitis B must synthesize mRNA, send it to the cytoplasm, and stuff it into the nucleocapsid where reverse transcriptase replicates the genome from mRNA. Not letting the mRNA out arrests viral replication.

Interferon. You won't see interferons-as-therapeutics very often. The one time in all of microbiology is going to be Hep B. Interferon makes the patient **experience flu-like symptoms**. And since Hep B treatments go on for **months**, it is one reason why the treatments fail—patients cannot tolerate it. We also don't know exactly how it works. We think it acts like local cytokines from an infected cell, telling nearby cells to get their defenses up. Learn "*interferon, Hep B, flu symptoms.*"

Ribavirin + interferon was the treatment for hepatitis B. RNA polymerase is a fairly ubiquitous enzyme. Every human cell with a nucleus uses it for transcription. But we got smarter, and decided to go after virus-specific enzymes with **nucleotide analogs** that inhibit **RdDp** (reverse transcriptase). We took the medications we used to treat HIV and used them on hepatitis B. Reverse transcriptase reads RNA to make DNA, degrades the RNA, and uses DNA to make DNA. That happens in the capsid, in the cytoplasm.

Lamivudine is a **cytosine analog** that **lacks the 3' OH group**. Where the acyclos had no pentose sugar at all, lamivudine has no hydroxyl group to form the pentose-phosphate backbone bond (between the 3' OH and the 5' phosphate of the incoming nucleotide). That means that once it is incorporated, there can be no further elongation of the chain. It has a strong affinity for **reverse transcriptase** (RdDp). Using our organizer, this is a polymerase inhibitor, and the polymerase it inhibits is reverse transcriptase (RdDp). When used on hepatitis B, it prevents the cytoplasmic activity which takes the mRNA transcript and turns it into dsDNA. **Entecavir** is a **guanosine analog** that doesn't have the oxygen

in the pentose group on the sugar. Other reverse transcriptase inhibitors, such as adefovir, tenofovir, and telbivudine work as nucleotide analogs, are turned on by viral enzymes, and affect primarily the cytoplasmic function of reverse transcriptase.

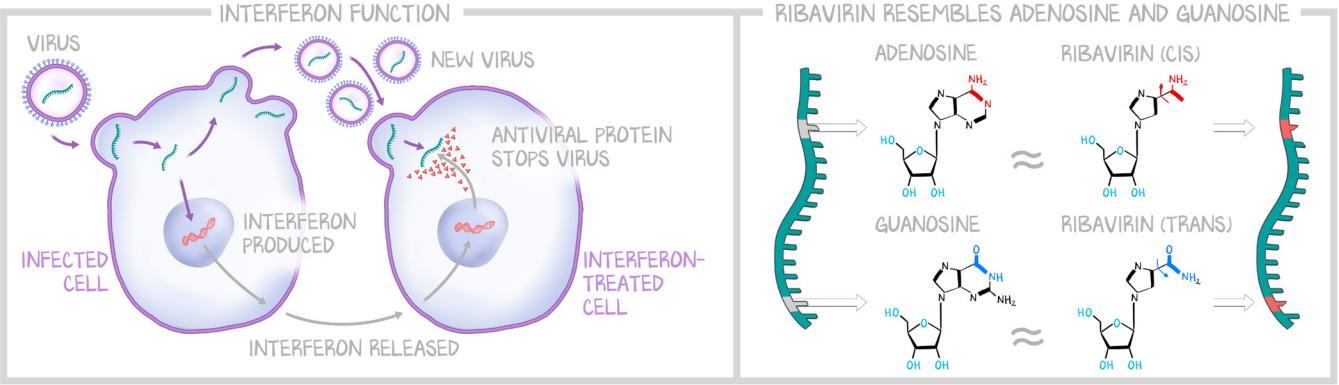

Figure 8.2: Drugs Used to Treat Hep B
(a) Interferon is normally released by virally infected cells, informing the neighbor cells a virus is nearby. Interferon induces transcription of proteins that prevent viral uncoating and penetration. Interferon's therapeutic use has fallen out of favor because of its poor efficacy and severe side effects. (b) Ribavirin is a nucleotide analog that can resemble either adenosine or guanosine. Its exact effect on polymerase inhibition has not been fully elucidated.

Medications That Treat Hep C

Until the 2010s, the inevitable conclusion of a patient infected with chronic hepatitis C was cirrhosis, end-stage liver disease. The chronic inflammation would eventually scar the liver. Treatment for Hep C was with a **year's worth** of ribavirin and interferon. A year's worth of feeling like you have the flu. And the cure rates were pretty poor. It worked for genotypes 2 and 3. Unfortunately, the predominant genotypes in the US are 1 and 4 (there is also a 5 and 6; this discussion is only to show you we needed something better than what we had).

We can now **cure 99% of Hep C** infections. With the advent of **direct-acting antivirals** (DAA), a generic term that refers to hepatitis C virally encoded enzymes specifically, we can now cure C. We've also discovered that Hep C is a pretty stupid virus—while certain combinations were better for certain genotypes, by combining any two mechanisms of action of Hep C antivirals (DAAs), Hep C is eradicated. There are four classes of DAAs: the nonstructural protein (NS) NS3/4A **protease** inhibitors, NS5B **nucleoside RNA polymerase inhibitors**, NS5B **non-nucleoside RNA polymerase inhibitors**, and NS5A inhibitors, whose mechanism of action is uncertain.

The nomenclature of the proteins initially seems intimidating. Take out the nonstructural protein part of each of those words, and what do you get? Protease inhibitors, nucleoside polymerase inhibitors, and non-nucleoside polymerase inhibitors. Just like everything we've studied so far, except we add a protease inhibitor. Because Hep C is a ss(+)RNA virus, the polymerase is going to be an RNA-dependent RNA polymerase (RdRp). RdRp is a viral enzyme only and so administration of these drugs against hepatitis C affects only the hepatitis C-infected cells.

You are not expected to know which medications fall into which classification. Hepatitis C has six genotypes, and certain medications work better for certain genotypes. This level of granularity would be absurd to expect a basic science student to know. The original DAAs, boceprevir, and telaprevir you should be able to recognize. They are hardly used anymore, because newer DAAs, even in the past five years, have eliminated the need for intravenous/intramuscular administration, and are now interferon-free (the initial regimens clung to the old ways a little while transitioning to DAA-only therapy).

Combination therapy is always superior to monotherapy. Most regimens involve the combination of an NS5A (the one we aren't sure how it works) with one of the others. NS5B polymerase inhibitors + NS5A inhibitors tend to have the widest genotype effect. NS3/4 protease inhibitor + NS5A affects genotypes 1 and 4, the genotypes that usually did not respond to ribavirin and interferon. If protease inhibitors are used, boost with ritonavir.

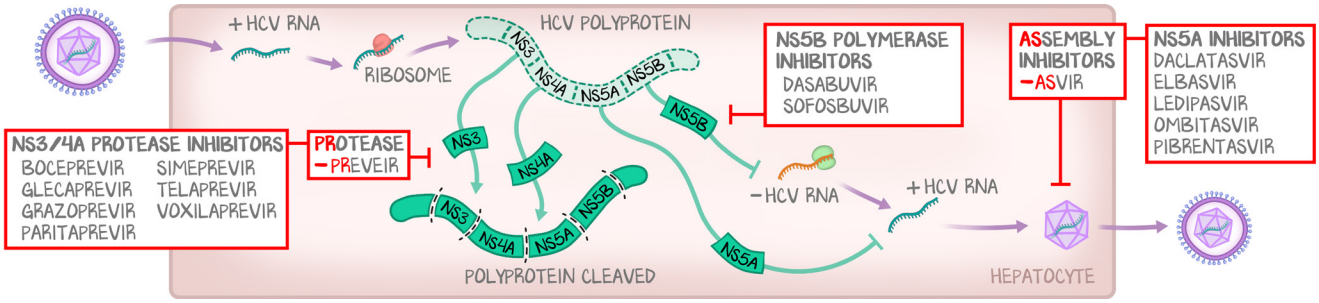

Figure 8.3: Mechanism of Action of Hep C Treatments
Hepatitis C codes for a single polyprotein. That polyprotein is then cleaved into individual proteins, each given a designation as a non-structural (NS) protein in the order they occur within the polyprotein. The polyprotein is cleaved by proteases. Proteases have been designated NS3 and NS4A. Therefore, NS3/4A inhibitors are protease inhibitors and so begin their suffix with pr for protease. Another component of that polyprotein that comes next in line is designated NS5A (following NS4A). NS5A is an assembly protein that facilitates the assembly of the virion. NS5A inhibitors are therefore assembly inhibitors and start their suffix with as for assembly. The last in line is NS5B (following NS5A). NS5B is the viral RdRp. So NS5B are polymerase inhibitors. Dasabuvir is a non-nucleotide polymerase inhibitor while sofosbuvir is a nucleotide analog.

HIV Life Cycle and Gene Review

GENE	PROTEIN	FUNCTION
gag	p24	Capsid protein, HIV screen is based on Ab to p24
pol	pol	Polymerase: reverse transcriptase
	int	Integrase
	pro	Protease
env	gp120	Surface protein binds to CD4, CXCR4, CCR5
	gp41	Viral fusion

Table 8.3: HIV Life Cycle and Therapeutic Targets

HIV is enveloped. The *env* gene codes for glycoproteins gp120 and gp41. gp120 binds to CD4 (its receptor) and to CCR5 (its receptor), deploying gp41. gp41 fuses the membrane of the virion and the cell, injecting the nucleocapsid and reverse transcriptase into the cytoplasm. The *pol* gene codes for reverse transcriptase (pol protein of *pol* gene) which transforms the ss(+)RNA virus genome into dsDNA, where it transports to the nucleus. The *pol* gene also codes for integrase (int protein of *pol* gene), which splices the viral genome into the host genome. HIV then directs transcription of the viral genome, making mRNA. If the mRNA is the entire length of the genome, it is deemed viral replication. If the mRNA is discrete genes, that mRNA is sent to the cytoplasm where the host ribosomes translate that mRNA into amino acid sequences. If the mRNA is of any other genes, protease (pro protein of *pol* gene) provides post-translational modification to produce the proteins of the virus, including p24

(p24 protein of the *gag* gene). The genome, capsid, and enzymes are shoved into an envelope, and the virus blebs off the plasma membrane.

Attachment and fusion is called entry. Entry inhibitors prevent entry.

Reverse transcriptase is the polymerase to target. Nucleoside analogs and non-nucleoside analogs inhibit it.

Integrase carries out the process of integration. Integrase inhibitors prevent integration.

Proteolytic processing is carried about by protease. Protease inhibitors prevent assembly of virions.

Budding and release are not targets for HIV medications.

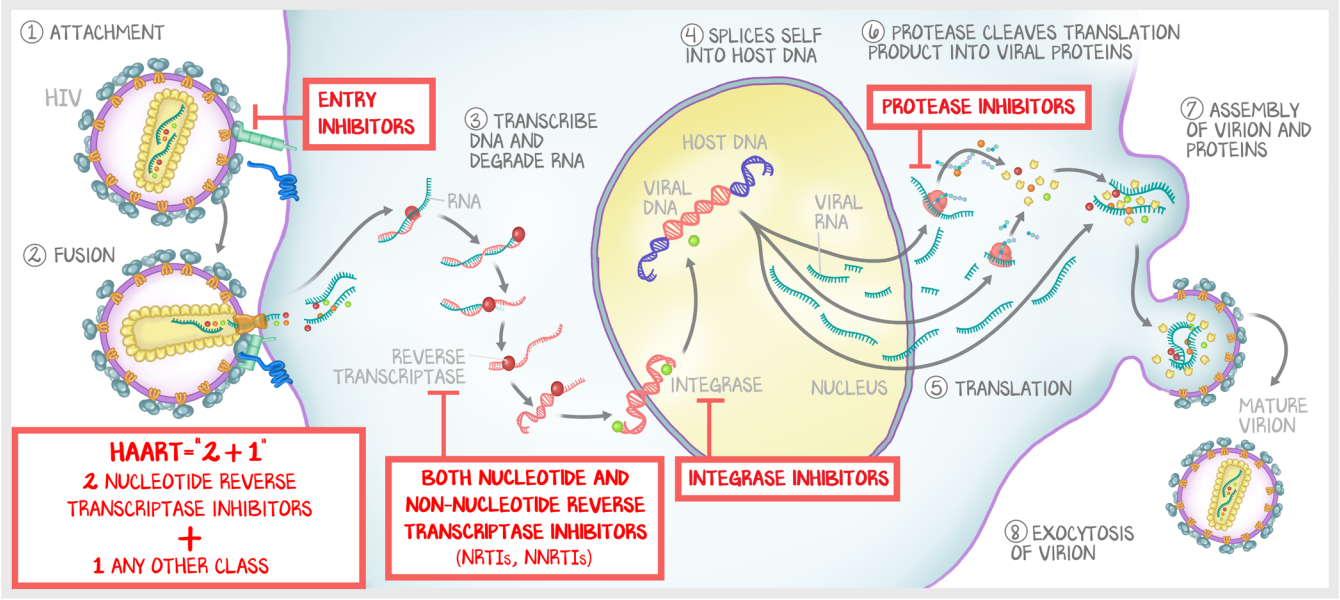

Figure 8.4: HIV Life Cycle and Therapeutic Targets
An overview of the mechanisms of HAART. There are many targets available during the HIV life-cycle. Effective therapy is deemed HAART. HAART consists of a 2+1 regimen. That is two nucleotide reverse transcriptase inhibitors and one of any other class. The decision is made based on genome sequencing and susceptibility testing. Refer back to this illustration as you proceed through the next several pages.

Medications Used to Treat HIV

Highly Active AntiRetroviral Therapy (HAART) is how we treat HIV. HAART is always "2+1." The 2 of "2+1" is two **nucleoside reverse transcriptase inhibitors** (nucleoside analog, RdDp inhibitors), abbreviated NRTIs. HAART is always **two** nucleoside reverse transcriptase inhibitors and one anything else. Nucleoside analogs target reverse transcriptase, and so target the product of the gene *pol*. Examples include tenofovir and emtricitabine (Truvada®) and abacavir + lamivudine (Epzicom®). Tenofovir and emtricitabine (Truvada®) is what the PrEP and PEP studies were conducted with.

The "+1" is **any** other class. HAART is started **at the time of diagnosis**. A genotype is performed, a sort of "viral culture and sensitivity" that provides information on mutations, which medications will work, and which will not. The combination therapy is chosen based on the patient's comorbid conditions, ease of adherence (three meds, one pill), and the genotype. You will not be selecting medication regimens in the basic sciences. You should be able to recognize certain medications. The classic medications are in the chart at the beginning of the lesson. This next one is not meant to be memorized, and serves to show the breadth of the treatments we have (and to break up this paragraph and the paragraphs on drug classes that follow).

NUCLEOSIDE ANALOGUES (NRTIS)	NNRTIS	PROTEASE INHIBITORS	ENTRY INHIBITORS	INTEGRASE INHIBITOR
Emtricitabine (FTC)	Efavirenz	Amprenavir/r	Enfuvirtide (gp120)	Raltegravir
Tenofovir (adenosine)		Atazanavir/r	Maraviroc (CCR5)	
		Darunavir/r		
Abacavir (ABC)	Rilpivirine	Indinavir/r		
Lamivudine (3TC)	Delavirdine	Lopinavir/r		
Stavudine (d4T)	Nevirapine	Nelfinavir/r		
Zalcitabine (ddC)		~~Ritonavir~~ (never alone)		
Zidovudine (AZT)				
Didanosine (ddI)				
Azidothymidine (AZT)				

Table 8.4: Long List of HIV Medications by Class

NRTI	NRTIS	+	1 OTHER	TRADE NAME
Emtricitabine	Tenofovir	+	Efavirenz	Atripla®
Emtricitabine	Tenofovir	+	Rilpivirine	Complera®
Abacavir	Lamivudine	+	Dolutegravir/r	Triumeq®
Any NRTI	Any NRTI	+	Any other class	HAART

Table 8.5: Examples of HAART-in-a-pill, and how 2+1 can work with combination of pills.
Abacavir/zidovudine/lamivudine (Trizivir®) is not HAART. It is three NRTIs at once. It is a combination pill. Many textbooks erroneously provide is as an example of HAART because it is three medications. It is an example of what we do not do, unless genotyping demands 3 NRTIs and something else.

DRUG	ASSOCIATION	DRUG	ASSOCIATION
Zidovudine AZT	**Pregnancy is safe**	Emtricitabine	Teratogenic
Didanosine	Pancreatitis (30%)	Efavirenz	Teratogenic, ↑ Cholester
Abacavir	Hypersensitivity (5% die)	Atazanavir	↑ Bilirubin

Table 8.6: Examples of Adverse Events

The first class used was **non-nucleoside reverse transcriptase inhibitors** (non-nucleoside analogs, RdDp inhibitors) abbreviated as NNRTIs. They target reverse transcriptase, the protein of gene *pol*. Examples include efavirenz (included with tenofovir and emtricitabine to form the 3-meds-in-1-pill Atripla®) and Rilpivirine (included with tenofovir and emtricitabine to form the 3-meds-in-1-pill Complera®).

All other classes are not inhibitors of polymerase. All others target something else the virus does. The backbone always remains two NRTIs + 1 other.

In practice, the most commonly used "+1" other than NNRTIs are the protease inhibitors. **Protease inhibitors** (end in "inavir") are reversible antagonists to HIV aspartyl **protease**, which is responsible for cleavage of the translated polyprotein into viral proteins. All protease inhibitors are **boosted with** 100 mg **of ritonavir** (itself a protease inhibitor) that prevents resistance without increasing toxicity, written [drug]/r. **Resistance to one protease inhibitor confers resistance to all protease inhibitors**. Commonly used drugs are darunavir/r and atazanavir/r. Atazanavir is Reyataz®; its side effect is elevated bilirubin, jaundice, turning patients yellow, like the rays of the sun. It targets the pro protein of gene *pol*.

There are only two **entry inhibitors**—enfuvirtide and maraviroc. **Enfuvirtide** binds to **gp41** in the viral envelope, preventing gp41 from fusing the plasma membranes, injecting the nucleocapsid into the cytoplasm. Specifically, Enfuvirtide is a fusion inhibitor. **Maraviroc** binds to the **CCR5-coreceptor** on the host cell side, interfering with gp120 coreceptor interaction necessary to deploy gp41. Technically, maraviroc is an attachment inhibitor. Since attachment, fusion, and uncoating go hand in hand, they are lumped together as entry inhibitors. Genetic testing for coreceptor tropism is required before choosing maraviroc (if this HIV goes for CXCR4 and not CCR5, there would be no point in choosing it). Resistance develops quickly to entry inhibitors, and they are not often first-line. Entry inhibitors target the product of gene *env*.

The **integrase inhibitors** grab onto host DNA so **viral integrase cannot** grab onto that DNA. In order to get the viral DNA into host DNA, integrase has to make some cuts to the host DNA, then insert the viral DNA. By having something else at the site where the integrase would normally cut, it has nothing to cut, so does nothing. Said biochemically, the active site of the integrase enzyme is occupied by a structural component. These can be identified by the "in-tegra-virus" suffix "-tegravir." Commonly used is Raltegravir. Integrase inhibitors target the int protein of the *pol* gene.

Pre-exposure prophylaxis (PrEP) combines tenofovir and emtricitabine, the backbone combination of many modern 2+1 regimens. Taken daily, it prevents the contraction of HIV. It should not be used as a substitute for safe sex practices—always wear a condom. But PrEP is greatly reducing the risk of HIV transmission. **Post-exposure prophylaxis** (PEP) uses the same combination for those with high-risk behavior, but with unknown history of infection—the person taking the PEP doesn't know if he or she has HIV or not. Clinical post-exposure prophylaxis, as occurs when a health care worker uses a needle on a patient with known HIV and then accidentally needles himself, uses 2+1 therapy, usually tenofovir, emtricitabine, and efavirenz.

AIDS

Acquired Immune Deficiency Syndrome (AIDS) is defined by a CD4 less than 200, or HIV plus the presence of any AIDS-defining illness. Even though the CD4 count may rise above 200, a patient that is diagnosed with AIDS keeps the title. Start treatment with HAART early to prevent AIDS.

INFECTION	CD4 COUNT	PROPHYLAXIS WITH
PCP	< 200	TMP/SMX Or dapsone Or atovaquone
Toxoplasmosis	< 100	TMP/SMX
Mycobacterium avium complex	< 50	Azithromycin weekly

Table 8.7